

Exhibit D

How SEX and GENDER Influence Health and Disease

Sex and gender can influence health in important ways. While sex and gender are distinct concepts, their influence is often inextricably linked. The scientific studies that generate the most complete data consider sex and/or gender influences in study design, data collection and analysis, and reporting of findings.

Sex is a biological classification, encoded in our DNA. Males have XY chromosomes, and females have XX chromosomes. Sex makes us male or female. Every cell in your body has a sex—making up tissues and organs, like your skin, brain, heart, and stomach. Each cell is either male or female depending on whether you are a man or a woman.

Gender refers to the socially constructed roles, behaviors, expressions, and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, and how they act and interact. Gender is usually conceptualized as binary (girl/woman and boy/man), yet there is considerable diversity in how individuals and groups understand, experience, and express it.

Visit [NIH.gov/women](https://nih.gov/women) to learn how studying sex and gender strengthens science.

Examples of **SEX** and **GENDER** influences

Mental health

-  Women are twice as likely as men to experience depression, with some women experiencing mood symptoms related to hormone changes during puberty, pregnancy, and perimenopause.
-  Women are more likely to admit to negative mood states and to seek treatment for mental health issues, in contrast to men.

Smoking cessation

-  Women have a harder time quitting smoking than men do. Women metabolize nicotine, the addictive ingredient in tobacco, faster than men. Differences in metabolism may help explain why nicotine replacement therapies, like patches and gum, work better in men than in women. Men appear to be more sensitive to nicotine's pharmacologic effects related to addiction.
-  Although men are more sensitive than women to nicotine's addiction-related effects, women may be more susceptible than men to non-nicotine factors, such as the sensory and social stimuli associated with smoking.

Cardiovascular risk

-  The blood vessels in a woman's heart are smaller in diameter and much more intricately branched than those of a man. Those differences offer one explanation for why women's vessels may become blocked in a different pattern than those in men. Women's heart attack symptoms and the patterns seen on a heart-screening test can differ, sometimes leading to a wrong diagnosis—or worse—missing the signs of an oncoming heart attack.
-  Women are often the primary caretakers of children, household needs, and aging family members, and they are more likely to delay prevention and treatment for chronic conditions like heart disease.

Osteoporosis

-  Osteoporosis is more common in women because they have less bone tissue than men and experience a rapid phase of bone loss due to hormonal changes at menopause.
-  Osteoporosis in men older than 50 can go undetected and is often undertreated because patients and providers think of osteoporosis as a “woman’s disease.”

Knee arthritis

-  Women and girls are more likely to injure their knees when playing sports, in part due to their knee and hip anatomy, imbalanced leg muscle strength, and looser tendons and ligaments. Knee injuries such as ACL tears dramatically increase a person's risk of developing osteoarthritis later in life.
-  Walking in high-heeled shoes increases stress on the knee joint, placing women at increased risk of developing osteoarthritis.